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<p style="text-align: center;">As printed</p> <b>(54) Title:</b> NOVEL LHRH ANTAGONISTS WITH IMPROVED SOLUBILITY CHARACTERISTICS <b>(54) Bezeichnung:</b> NEUE LHRH-ANTAGONISTEN MIT VERBESSERTEN LÖSLICHKEITSEIGENSCHAFTEN  <b>(57) Abstract</b> <p>The invention relates to peptides which contain N-methylated amino acid building blocks and are provided with improved water solubility. Medicaments containing the inventive peptides can be used for the treatment of hormone-dependent tumours and hormone-influenced, non-malignant diseases.</p> <b>(57) Zusammenfassung</b> <p>Die Erfindung betrifft Peptide, die N-methylierte Aminosäurebausteine enthalten und eine verbesserte Wasserlöslichkeit aufweisen. Arzneimittel, in denen die erfindungsgemässen Peptide enthalten sind, können zur Behandlung hormonabhängiger Tumore und hormonbeeinflusster nicht-maligner Erkrankungen verwendet werden.</p>		

Novel LHRH antagonists having improved solubility  
properties

The invention relates to LHRH antagonists having  
5 improved solubility properties, processes for the  
preparation of these compounds, medicaments in which  
these compounds are contained, and the use of the  
medicaments for the treatment of hormone-dependent  
tumours and hormone-influenced non-malignant disorders  
10 such as benign prostate hyperplasia (BPH) and  
endometriosis.

The nomenclature used for the definition of the  
peptides agrees with that nomenclature explained by the  
15 IUPAC-IUB Commission on Biochemical Nomenclature  
(European J. Biochem. 1984, 138, 9-37), in which, in  
agreement with the conventional representation, the  
amino groups at the N terminus appear to the left and  
the carboxyl group at the C terminus appears to the  
20 right. The LH-RH antagonists such as the peptides  
according to the invention include naturally occurring  
and synthetic amino acids, the former including Ala,  
Val, Leu, Ile, Ser, Thr, Lys, Arg, Asp, Asn, Glu, Gln,  
Cys, Met, Phe, Tyr, Pro, Trp and His. The abbreviations  
25 for the individual amino acid residues are based on the  
trivial names of the amino acids and are Ala=alanine,  
Arg=arginine, Gly=glycine, Leu=leucine, Lys=lysine,  
Pal(3)=3-(3-pyridyl)alanine, Nal(2)=3-(2-naphthyl)-  
alanine, Phe=phenylalanine, Cpa=4-chlorophenylalanine,  
30 Pro=proline, Ser=serine, Thr=threonine, Trp=tryptophan,  
Try=tyrosine and Sar=sarcosine. All amino acids  
described here originate from the L series, if not  
mentioned otherwise. For example, D-Nal(2) is the  
abbreviation for 3-(2-naphthyl)-D-alanine and Ser is  
35 the abbreviation for L-serine. Substitutions on the  $\epsilon$   
amino group in the side chain of lysine are represented  
by a term placed in brackets behind Lys, if appropriate  
in the form of an abbreviation.

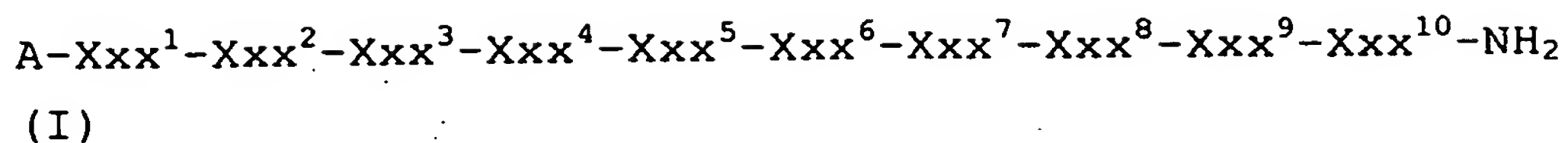
The first series of potent antagonists was obtained by the introduction of aromatic amino acid residues into the positions 1, 2, 3 and 6 or 2, 3 and 6. The customary way of writing the compounds is as follows:  
5 the amino acids are first indicated which have taken the place of the amino acids originally present in the peptide chain of LH-RH, the positions in which the exchange took place being marked by superscripted figures. Furthermore, by the notation "LH-RH" placed  
10 afterwards it is expressed that these are LH-RH analogues in which the exchange has taken place.

Known antagonists are:

[Ac-D-Cpa<sup>1,2</sup>, D-Trp<sup>3,6</sup>] LH-RH (D.H. Coy et al., In:  
15 Gross, E. and Meienhofer, J. (Eds) Peptides; Proceedings of the 6th American Peptide Symposium, pp. 775-779, Pierce Chem. Co., Rockville III. (1979):  
[Ac-Pro<sup>1</sup>, D-Cpa<sup>2</sup>, D-Nal(2)<sup>3,6</sup>] LH-RH (US Patent No. 4,419,347) and [Ac-Pro<sup>1</sup>, D-Cpa<sup>2</sup>, D-Trp<sup>3,6</sup>] LH-RH  
20 (J.L. Pineda, et al., J. Clin. Endocrinol. Metab. 56, 420, 1983).

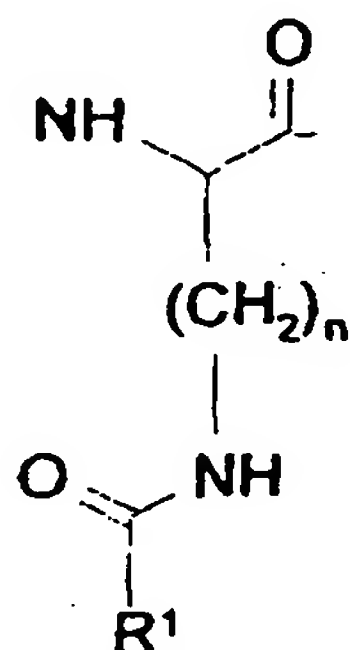
In order to improve the action of antagonists, basic amino acids, for example D-Arg, were later introduced  
25 into the 6 position. For example [Ac-D-Cpa<sup>1,2</sup>, D-Trp<sup>3</sup>, D-Arg<sup>6</sup>, D-Ala<sup>10</sup>] LH-RH (ORG-30276) (D.H. Coy, et al., Endocrinology 100, 1445, 1982); and  
[Ac-D-Nal(2)<sup>1</sup>, D-Phe(4-F)<sup>2</sup>, D-Trp<sup>3</sup>, D-Arg<sup>6</sup>] LH-RH (ORF 18260) (J.E. Rivier et al., in: Vickery B.H. Nestor, Jr. J.J., Hafez, E.S.E (Eds). LHRH and its Analogs,  
30 pp. 11-22 MTP Press, Lancaster, UK 1984).

Further potent LH-RH antagonists are described in WO 92/19651, WO 94/19370, WO 92/17025, WO 94/14841,  
35 WO 94/13313, US-A 5,300,492, US-A 5,140,009, EP 0 413 209 A1 and DE 195 44 212 A1.



in which

- 5 A is an acetyl or a 3-(4-fluorophenyl)propionyl group,  
 Xxx<sup>1</sup> is D-Nal(1) or D-Nal(2),  
 Xxx<sup>2</sup>-Xxx<sup>3</sup> is D-Cpa-D-Pal(3) or a single bond,  
 Xxx<sup>4</sup> is Ser,  
 Xxx<sup>5</sup> is N-Me-Tyr,  
 10 Xxx<sup>6</sup> is D-Cit, D-Hci or a D-amino acid group of the  
 general formula (II)

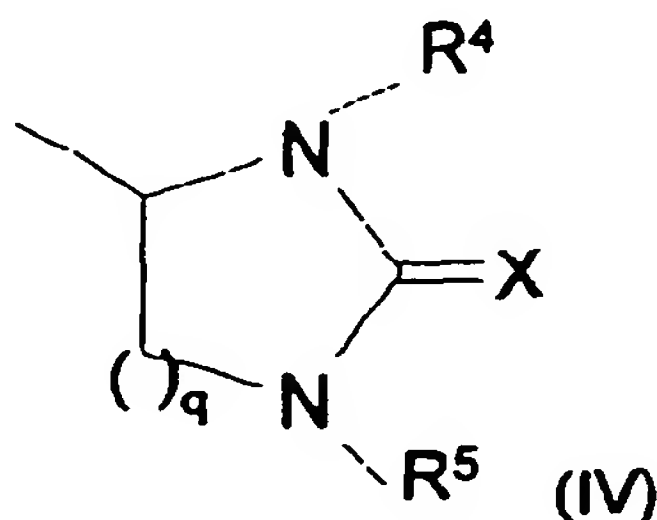


(II)

- 15 in which n is the number 3 or 4, where R<sup>1</sup> is a group  
 having the general formula III



- 20 where p is an integer from 1 to 4, R<sup>2</sup> is hydrogen or an  
 alkyl group and R<sup>3</sup> is an unsubstituted or substituted  
 aryl group or heteroaryl group, or R<sup>1</sup> is a 3-amino-  
 1,2,4-triazole-5-carbonyl group or R<sup>1</sup> is a ring of the  
 general formula (IV)



The compounds according to the invention can be used for the treatment of hormone-dependent tumours, in particular prostate carcinoma or breast cancer, and  
5 also for non-malignant indications whose treatment necessitates LH-RH hormone suppression. For this, they are mixed with the customary vehicles and excipients and formulated as medicaments.

10 The synthesis of compounds according to formula (I) can both be carried out either by classical fragment condensation or by solid-phase synthesis according to Merrifield with synthesis following one another using D-lysine already acylated in the side chain with the  
15 carboxylic acid of the general formula  $R^1\text{-COOH}$  or by reaction of a decapeptide unit with the appropriate carboxylic acids by amide linkage in the side chain of D-lysine<sup>6</sup>. Accordingly, the introduction of the  $R^1\text{-CO-}$  group can be performed in three different positions in  
20 the process: before the condensation of the individual units to give the peptide, after the incorporation of lysine or ornithine in the peptide chain, but before the condensation of the next unit or after condensation of all units.

25 The compounds of the formula (I) are synthesized according to the known methods, such as, for example, by pure solid-phase technique, partly solid-phase technique (so-called fragment condensation) or by the  
30 classical solution couplings (see M. Bodanszky, "Principles of Peptide Synthesis", Springer Verlag 1984).

For example, the methods of solid-phase synthesis are described in the textbook "Solid Phase Peptide  
35 Synthesis", J.M. Stewart and J.D. Young, Pierce Chem. Company, Rockford, III, 1984, and in G. Barany and R.B. Merrifield "The Peptides", Ch. 1, pp. 1-285, 1979, Academic Press Inc. Classical solution syntheses are

Esters of N-protected amino acids, such as, for example, N-hydroxysuccinimide esters or 2,4,5-trichlorophenyl esters, are particularly highly suitable for the stepwise condensation of amino acids.

5 The aminolysis can be very well catalysed by N-hydroxy compounds which have approximately the acidity of acetic acid, such as, for example, 1-hydroxybenzotriazole.

10 Intermediate amino protective groups which present themselves are groups which are removed by hydrogenation, such as, for example, the benzyloxycarbonyl radical (= Z radical) or groups which can be removed by weak acid. Suitable protective groups  
15 for the  $\alpha$ -amino groups are, for example:

tertiary butyloxycarbonyl groups, fluorenylmethyloxycarbonyl groups, carbobenzoxy groups or carbobenzothio groups (if appropriate in each case having a p-bromo [sic] or p-nitrobenzyl radical), the  
20 trifluoroacetyl group, the phthalyl radical, the o-nitrophenoxyacetyl group, the trityl group, the p-toluenesulphonyl group, the benzyl group, benzyl radicals substituted in the benzene nucleus (p-bromo [sic] or p-nitrobenzyl radical) and the  $\alpha$ -phenylethyl  
25 radical. Reference is also made here to P. Greenstein and Milton Winitz, Chemistry of Amino Acids, New York 1961, John Wiley and Sons, Inc., Volume 2, for example page 883 et seq., "Principles of Peptide Synthesis", Springer Verlag 1984, "Solid Phase Peptide Synthesis",  
30 J.M. Stewart and J.D. Young, Pierce Chem. Company, Rockford, III, 1984, G. Barany and R.B. Merrifield "The Peptides", Ch. 1, pp. 1-285, 1979, Academic Press Inc., and also The Peptides, Volume 2, Ed. E. Gross and J. Maierhofer, Academic Press, New York. These  
35 protective groups are fundamentally also suitable for the protection of further functional side groups (OH groups,  $\text{NH}_2$  groups) of the corresponding amino acids.



swollen in organic solvents (for example a copolymer of polystyrene and 1% divinylbenzene). The synthesis of a protected decapeptide amide on a methylbenzhydrylamide [sic] resin (MBHA resin, i.e. polystyrene resin provided with methylbenzhydrylamide [sic] groups), which affords the desired C-terminal amide function of the peptide after HF cleavage from the support, can be carried out according to the following flow diagram:

10 Flow diagram  
Peptide synthesis protocol

Stage	Function	Solvent/Reagent (v/v)	Time
1	Washing	Methanol	2 × 2 min
2	Washing	DCM	3 × 3 min
3	Removal	DCM/TFA (1:1)	1 × 30 min
4	Washing	Isopropanol	2 × 2 min
5	Washing	Methanol	2 × 2 min
6	Washing	DCM	2 × 3 min
7	Neutralization	DCM/DIPEA (9:1)	3 × 5 min
8	Washing	Methanol	2 × 2 min
9	Washing	DCM	3 × 3 min
10	STOP	Addition of the Boc-As in DCM + DIC + HOBt	
11	Coupling	DCM, optionally DCM/DCF	approx. 90 min
12	Washing	Methanol	3 × 2 min
13	Washing	DCM	2 × 3 min

The N $\alpha$ -Boc-protected amino acids are customarily coupled in a three fold molar excess in the presence of diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) in CH<sub>2</sub>Cl<sub>2</sub>/DMF in the course of 90 min, and the Boc-protected group is removed by action of 50% trifluoroacetic acid (TFA) in CH<sub>2</sub>Cl<sub>2</sub> for half an hour. To check for complete conversion, the chloranil test according to Christensen and the Kaiser's ninhydrin test can be used. Radicals of free amino function [sic]

The following examples serve to illustrate the invention without restricting it.

Example 1

5

Ac-D-Nal(2)<sup>1</sup>-D-Cpa<sup>2</sup>-D-Pal(3)<sup>3</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Hci<sup>6</sup>-Nle<sup>7</sup>-  
Arg<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>

10 The synthesis was carried out according to a solid-phase flow diagram (Peptide Synthesis Protocol, p. 11) with DIC/HOBt coupling, starting from 3.3 g of MBHA resin (loading density 1.08 mmol/g). After HF cleavage from the polymeric support, 3.4 g of crude peptide were obtained, which were purified by standard processes of  
15 preparative HPCI [sic]. After subsequent freeze-drying, 1.43 g of HPLC-uniform product of the empirical formula C<sub>72</sub>, H<sub>96</sub>, N<sub>17</sub>, O<sub>14</sub>, Cl [sic] having correct FAB-MS: 1458.7 (M+H<sup>+</sup>) (calc: 1457.7), and corresponding <sup>1</sup>H-NMR spectrum were obtained.

20

<sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O/DMSO-d<sub>6</sub>, δ in ppm):

8.7 to 7.2, several m, arom. H and incompletely  
exchanged NH; 6.92 and 6.58, 2d, 2x2H, arom. H p-Cl-  
Phe; 5.2 to 3.5, several m, Cα-H and aliph. H; 3.2 to  
25 2.6, several m, aromat. Cβ-H 2.1 to 0.7, several m,  
residual aliphatic. H; 1.70, s, 3H, acetyl; 1.20, d, 3H,  
Cβ-H Ala; 0.8, m, Cδ-H Leu

Example 2

30

Ac-D-Nal(2)<sup>1</sup>-D-Cpa<sup>2</sup>-D-Pal(3)<sup>3</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Lys(B)<sup>6</sup>-  
Leu<sup>7</sup>-Lys(iPr)<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>

35 The synthesis was carried out according to a flow diagram (Peptide Synthesis Protocol, p. 11) with DIC/HOBt coupling, starting from 4.0 g of MBHA resin (loading density 1.11 mmol/g). After HF cleavage from the polymeric support, 4.87 g of crude peptide were



empirical formula C<sub>82</sub>, H<sub>106</sub>, N<sub>19</sub>, O<sub>15</sub>, Cl [sic] having correct ESI-MS: 1632.7 (M+H<sup>+</sup>) (calc: 1631.7), and corresponding <sup>1</sup>H-NMR spectrum were obtained.

5 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>, δ in ppm):  
10.4, s, 1H and 9.15, s, 2H, and 9.0, s, 2H, NHs of  
4-amidinoaniline; 8.60, m, 2H, arom. H; 8.3 to 7.2,  
several m, arom. H and NH; 7.27 and 7.20, 2d, 4H, arom.  
H (pCl)Phe; 6.96 and 6.60, 2d, 4H, arom. H Tyr; 5.2 to  
10 3.5, several m, Cα-H and aliphatic. H; 3.2 to 2.4,  
several m, Cβ-H and N-CH<sub>3</sub>; 2.1 to 1.1, several m,  
residual aliphatic. H; 1.70, s, 3H, acetyl; 1.20, d, 3H,  
Cβ-H Ala; 0.85, dd, 6H, Cδ-H Leu

15 Example 4

Ac-D-Nal(2)<sup>1</sup>-D-Cpa<sup>2</sup>-D-Pal(3)<sup>3</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Hci<sup>6</sup>-Nle<sup>7</sup>-  
Lys(iPr)<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>

20 The synthesis was carried out according to a solid-  
phase flow diagram (Peptide Synthesis Protocol, p. 11)  
with DIC/HOBt coupling, starting from 2.5 g of MBHA  
resin (loading density 1.08 mmol/g). After HF cleavage  
from the polymeric support, 2.78 g of crude peptide  
25 were obtained, which were purified by standard  
processes of preparative HPCI [sic]. After subsequent  
freeze-drying, 400 mg of HPLC-uniform product of the  
empirical formula C<sub>75</sub>, H<sub>102</sub>, N<sub>15</sub>, O<sub>14</sub>, Cl [sic] having  
correct ESI-MS: 1472.6 (M+H<sup>+</sup>) (calc: 1471.7), and  
30 corresponding <sup>1</sup>H-NMR spectrum were obtained.

<sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O/DMSO-d<sub>6</sub>, δ in ppm):  
8.62, m, 2H, 8.30, m, 2H, 7.80, m, 4H, 7.66, s, 1H,  
7.47, m, 2H, 7.36, d, 1H, arom. H; 7.25 and 7.20,  
35 2 d, 4H, arom. H (pCl)Phe; 6.96 and 6.63, 2d, 4H,  
arom. H Tyr; 5.10 to 4.0, several m, Cα-H and  
aliphatic. H; 3.75 to 2.65, several m, Cβ-H and N-CH<sub>3</sub>;  
2.1 to 1.05, several m, residual aliphatic. H; 1.74, s,

Example 6

3-(4-Fluorophenyl)propionyl-D-Nal(1)<sup>1</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Lys(Atz)<sup>6</sup>-Leu<sup>7</sup>-Arg<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>

5

The synthesis was carried out according to a solid-phase flow diagram (Peptide Synthesis Protocol, p. 11) with DIC/HOBt coupling, starting from 9.2 g of MBHA resin (loading density 1.08 mmol/g). After HF cleavage  
10 from the polymeric support, 5.8 g of crude peptide were obtained, which were purified by standard processes of preparative HPLC [sic]. After subsequent freeze-drying, 2.0 g of HPLC-uniform unsubstituted octapeptide were obtained, of which 0.4 mmol was reacted with 0.5 mmol  
15 of 3-amino-1,2,4-triazole-5-carboxylic acid in the presence of PyBOP as a coupling reagent to give 790 mg of crude product of the desired compound. After fresh HPLC purification, 200 mg of target compound of the empirical formula C<sub>64</sub>, H<sub>86</sub>, N<sub>17</sub>, O<sub>12</sub>, F [sic] having  
20 correct FAB-MS: 1304.6 (M+H<sup>+</sup>) (calc: 1303.6) were obtained.

<sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O/DMSO-d<sub>6</sub>, δ in ppm):

8.14, m, 1H, 7.90, m, 1H, 7.80, m, 1H, 7.50, m, 2H,  
25 7.35, m, 2H, 7.0, m, 6H, 7.63, m, 2H, aromat. H; 5.0, m, 1H, 4.83, m, 2H, 4.41, m, 1H, 4.30 - 4.05, several m, 4H, Cα-H; 3.66 to 2.25, several m, aliphatic and  
aromat. side-chain H; 2.95, s, and 2.75, s, N-Me; 2.05 to 1.1, several m, residual aliphatic. H; 1.20, d, Cβ-H  
30 Ala; 0.75, m, 6H, Cδ-H Leu

The compounds according to formula I according to the invention were investigated for their receptor binding. The process closely followed the process described in  
35 Beckers et al., Eur. J. Biochem. 231, 535-543 (1995). Cetrorelix obtained according to the synthesis disclosed above was iodinated with [<sup>125</sup>I] (Amersham; specific activity 80.5 Bq/fmol) using the IodoGen

NaCl/P<sub>i</sub> (137 mM NaCl, 2.7 mM KCl, 8.1 mM Na<sub>2</sub>HPO<sub>4</sub>,  
11.47 mM KH<sub>2</sub>PO<sub>4</sub>)/1 mM EDTA and collected by  
centrifugation. The cell pellet was resuspended in  
binding buffer (DMEM without H<sub>2</sub>CO<sub>3</sub>, with 4.5 g/l of  
5 glucose, 10 mM Hepes pH 7.5, 0.5% (mass/volume) BSA,  
1 g/l bacitracin, 0.1 g/l SBTI, 0.1% (mass/volume)  
NaN<sub>3</sub>). For displacement assays, 0.25 × 10<sup>6</sup> cells/100 µl  
were incubated with approximately 225 pM of the [<sup>125</sup>I]-  
cetrorelix (specific activity 5-10 × 10<sup>5</sup> dpm/pmol) and  
10 various concentrations of unlabelled compound according  
to the invention as competitor. The cell suspension in  
100 µl of binding medium was layered in 400 µl assay  
tubes over 200 µl of 84% by volume silicone oil (Merck  
Type 550)/16% by volume paraffin oil. After incubation  
15 for 1 h at 37°C with slow, continuous shaking, the  
cells were separated from the incubation medium by  
centrifugation for 2 min at 9000 rpm (rotor type  
HTA13.8; Heraeus Sepatec, Osterode/Germany). The tips  
of the tubes which contained the cell pellet were cut  
20 off. Cell pellet and supernatants were then analysed by  
counting the γ radiation. The amount of non-  
specifically bound material was determined at a final  
concentration of 1 µM with inclusion of unlabelled  
cetrorelix and was typically ≤ 10% of the total bound  
25 material. The analysis of the binding data was carried  
out using the EBDA/ligand analysis programme (Biosoft  
V3.0).

#### Method 2.

30

Functional assay for the determination of the  
antagonistic activity

The assay was carried out, provided with some  
35 modifications, as described in Beckers, T., Reiländer,  
H., Hilgard, P. (1997) "Characterization of  
gonadotropin-releasing hormone analogs based on a  
sensitive cellular luciferase reporter gene assay",

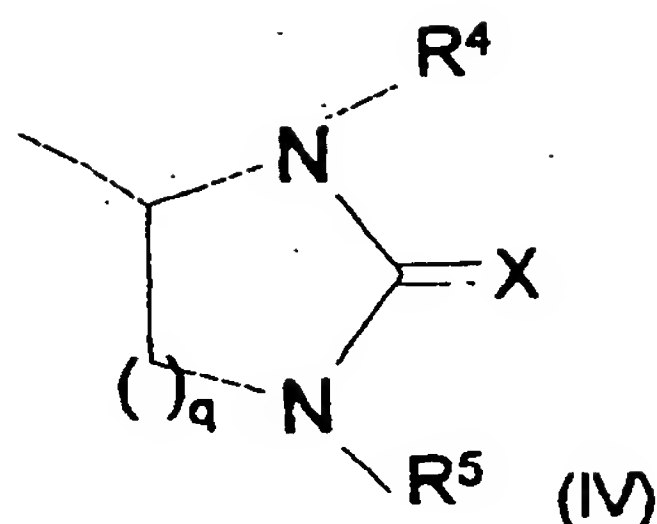
In this way, the following in-vitro data were obtained,  $K_D$  being the binding affinities and  $IC_{50}$  being the functional activity and pM being picomoles per litre:

5

Compound	$K_D$ [pM]	$IC_{50}$ [pM]
cetrorelix	170 (21)	198 (5)
Example 1 (Acetate salt)	n.d.	242 (3)
Example 2	181 (1)	684 (2)
Example 3	154 (1)	492 (2)
Example 6	n.d.	221 (2)

n.d. = not determined

() = number of independent experiments



in which q is the number 1 or 2, R<sup>4</sup> is a hydrogen atom or an alkyl group, R<sup>5</sup> is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, Xxx<sup>7</sup> is Leu or Nle, Xxx<sup>8</sup> is Arg or Lys(iPr), Xxx<sup>9</sup> is Pro and Xxx<sup>10</sup> is Ala or Sar, and their salts with pharmaceutically acceptable acids.

2. Compounds according to Claim 1, in which the salt is an acetate, trifluoroacetate or embonate.
3. Compounds according to Claim 1 or 2, in which Xxx<sup>6</sup> is D-[ε-N'-(imidazolidin-2-on-4-yl)formyl]-Lys, D-(3-amino-1,2,4-triazole-3-carbonyl)-Lys, abbreviated D-Lys(Atz) or D-[ε-N'-4-(4-amidino-phenyl)amino-1,4-dioxobutyl]-Lys, abbreviated D-Lys(B).
4. Compound according to Claim 1 having the formula:  
Ac-D-Nal(2)<sup>1</sup>-D-Cpa<sup>2</sup>-D-Pal(3)<sup>3</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Hci<sup>6</sup>-Nle<sup>7</sup>-Arg<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>.
5. Compound according to Claim 1 having the formula:  
Ac-D-Nal(2)<sup>1</sup>-D-Cpa<sup>2</sup>-D-Pal(3)<sup>3</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Lys(Atz)<sup>6</sup>-Leu<sup>7</sup>-Arg<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>.
6. Compound according to Claim 1 having the formula:  
Ac-D-Nal(2)<sup>1</sup>-D-Cpa<sup>2</sup>-D-Pal(3)<sup>3</sup>-Ser<sup>4</sup>-N-Me-Tyr<sup>5</sup>-D-Lys(B)<sup>6</sup>-Leu<sup>7</sup>-Lys(iPr)<sup>8</sup>-Pro<sup>9</sup>-D-Ala<sup>10</sup>-NH<sub>2</sub>.

14. Use of the substances according to Claims 1 to 11  
for producing medicaments for the treatment of  
hormone-dependent tumours, in particular prostate  
carcinoma or breast cancer, and also for non-  
5 malignant indications whose treatment necessitates  
LH-RH hormone suppression.
15. Process for producing medicaments, in which  
compounds according to Claims 1 to 11 are mixed  
10 with the customary vehicles and excipients and  
formulated as medicaments.